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14. ABSTRACT Despite considerable research on health issues affecting the nearly 700,000 U.S. veterans of the 1991 Persian Gulf War, fundamental questions and challenges remain. There is still no widely-accepted case definition for Gulf War illness (GWI) and little current information related to its characteristics. Nor has there been a comprehensive assessment of rates of more familiar diagnosed medical conditions. Gulf War veterans—many still looking for answers about unexplained health problems—have been anxious to participate in studies, while researchers commonly report enormous difficulty identifying adequate numbers of Gulf War veterans for their studies. This project addresses these challenges with a coordinated research effort. Investigators at Baylor University are using a multifaceted survey research strategy to obtain current information on symptoms and medical conditions from a nationally representative sample of 5,000 1991 Gulf War era veterans. These data will be used to optimize a GWI case definition, based on current symptoms, and to provide insights concerning rates of other medical conditions in Gulf War veterans. Parallel to this effort, the project is inviting a broad national sample of Gulf War era veterans to complete health questionnaires by mail or online, and to participate in the 1991 Veterans Research and Information Network (91VetNet), a national research and information resource for Gulf War era veterans and for investigators.					
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**Establishing a 1991 Veterans Research Network
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Introduction

Despite considerable research on health issues affecting U.S. veterans of the 1990-1991 Persian Gulf War, fundamental questions remain about the health consequences of military service in that conflict. The signature health problem associated with 1991 Gulf War military service has been Gulf War illness (GWI), the complex of undiagnosed symptoms that have persisted, for many veterans, for over 20 years. Studies indicate that at least one in four veterans are affected by a generally consistent pattern of excess symptoms, variously defined, that is not attributable to established medical or psychiatric diagnoses, and not explained by clinical diagnostic tests.¹⁻⁴ This problem has long been the focus of scientific studies, Congressional inquiries, media reports, and scientific review panels.

The need for current population health data to support an evidence-based Gulf War illness case definition. The GWI symptom profile typically includes some combination of cognitive difficulties, widespread pain, and unexplained fatigue—accompanied, in many veterans, by chronic digestive problems, respiratory difficulties, and skin abnormalities. Because there are no objective tests that can be used to diagnose GWI, it is currently identified only on the basis of veterans' symptoms. More than 20 years after Desert Storm, however, there is still no widely-accepted case definition for GWI. The 2008 report of the federal Research Advisory Committee on Gulf War Veterans' Illnesses describes eight different approaches used by different investigators to define or characterize GWI.¹ Some case definitions have characterized GWI either very broadly,⁵⁻⁷ or very narrowly,⁸⁻⁹ and most were not developed in a systematic, data-driven manner. Despite hundreds of research studies conducted in this population, the lack of a consistent, evidence-based GWI case definition has made study results difficult to interpret and compare and has slowed progress in addressing this problem. Further, there is little available information related to current characteristics of GWI or its impact on the lives of Gulf War veterans.¹⁰

The need for systematic, population-based data on other medical conditions affecting 1990-1991 Gulf War era veterans. Although GWI has been the most prominent health concern associated with the 1991 Gulf War, it is not the only condition of importance. More than 20 years after the war, however, there have been no published studies that provide systematic assessments, in nationally representative samples, of rates at which more familiar diagnosed medical conditions affect 1991 Gulf War veterans.¹⁰ Several studies have reported that 1991 Gulf War veterans have an excess rate of amyotrophic lateral sclerosis (ALS),¹¹⁻¹³ compared to nondeployed veterans of the same era, and one study has provided an indication that 1991 Gulf War veterans suffer from an elevated rate of lung cancer.¹⁴ Mortality studies have also reported that the subgroup of Gulf War veterans potentially exposed to nerve agents in connection with the 1991 Khamisiyah demolitions have died from brain cancers at twice the rate of unexposed veterans.^{15,16}

Overall, however, rates of most medical conditions have never been ascertained in 1991 Gulf War veterans. This includes multiple sclerosis, for which a great deal of concern has been raised by Congressional committees, and by veterans' advocates. Data on rates of medical diagnoses in this population are urgently needed, and not only for the insights this information can provide for

veterans and their healthcare providers. In a very practical sense, federal agencies and scientific review panels rely on studies of this type to establish healthcare policies and programs and to determine if veterans should receive disability compensation for diseases that may be related to their military service. Due to the lack of systematic research on diagnosed medical conditions in Gulf War veterans, data are not available to inform veterans, healthcare providers, and policymakers whether U.S. Gulf War veterans are affected by excess rates of most medical conditions of possible concern.

The need for an information resource for 1990-1991 Gulf War veterans and a mechanism to assist investigators in recruiting Gulf War-era veterans for research studies. Scientists conducting research on health issues associated with service in the 1990-1991 Gulf War often face serious challenges in carrying out quality research in an effective and efficient manner. This includes an unfortunate dichotomy with respect to recruitment of 1991 Gulf War era veterans for research studies. On one hand, nearly all investigators report enormous difficulty identifying adequate numbers of symptomatic and healthy Gulf War veterans for studies investigating laboratory markers, treatments, and other clinical parameters. As a result, investigators often have no choice but to enroll nearly all veterans they can identify through any means, yielding less-than-ideal study samples that may not be representative of ill veterans more generally. On the other hand, veterans and researchers commonly indicate that Gulf War veterans *want* to participate in studies. Unfortunately, though, there is no unified national veterans group or central contact point that can provide 1991 Gulf War era veterans with information related to research or other issues relevant to military service of this period. Veterans of this era, many still seeking answers about unexplained health conditions, are willing and even anxious to participate in research studies, but generally do not know that such studies are being conducted or that they are eligible to participate.

Project Overview. Investigators at Baylor University have designed the current project to address these prominent issues with a coordinated effort that utilizes a multipart, national sampling and state-of-the-art survey research strategy. This includes a Computer-Assisted Telephone Interview (CATI) survey of a nationally representative sample of 5,000 1991 Gulf War era veterans, under a contract arrangement with Westat. The CATI survey is designed to provide current data on symptoms and diagnosed medical conditions reported by 3,000 1991 Gulf War veterans, and 2,000 veterans of the same era who did not deploy to the Gulf War theater. In broad consultation with experts in the field, these data will be used to optimize a GWI case definition, based on veterans' current health status, and to provide important insights concerning rates of diagnosed medical conditions in Gulf War era veterans.

The project is also obtaining health data from a second, larger sample, referred to as the network sample. This involves contacting 45,000 Gulf War era veterans to invite them to complete health questionnaires by mail or online. These data will be used to further evaluate patterns observed in the CATI sample, including associations between health outcomes and deployment experiences. In addition, veterans in both the CATI and network samples are invited to participate in the 1991 Veterans Research and Information Network (91VetNet). Participating veterans will receive current information on health issues relevant to military service during 1990-1991 and will be notified about studies for which they may be eligible. The network will also serve as a resource

for scientists conducting research on the health of 1991-era veterans that can assist them in recruiting veterans who may be interested in participating in studies.

Overall, the project is designed to provide current, nationally representative data to identify the prevalence and characteristics of GWI, as well as rates of diagnosed diseases reported by 1991-era veterans. These data will be used to inform veterans, providers, and policymakers, and will also be used to optimize an evidence-based case definition of GWI. In addition, the project will provide a current information resource for 1991-era veterans and a recruitment resource for investigators conducting studies in this population. This is expected to have a positive impact on the broader Gulf War research effort, improving studies to advance GWI treatments and diagnostic tests, and provide insights into its pathobiology.

Body

Task 1. Prepare and Submit Documents to Obtain Regulatory Approvals

This project requires review and approval by the Baylor Institutional Review Board (IRB) and by the USAMRMC's Office of Human Research Protections (HRPO). We also initially understood, based on information provided by DOD officials, that the project would require review and approval by the federal Office of Management and Budget (OMB), under the federal Paperwork Reduction Act (PRA). We were informed that the OMB approval process typically requires a minimum of eight months. We therefore designed the project timeline to allow ten months for obtaining regulatory approvals, as indicated in the Statement of Work.

Our initial strategy was to begin the process and document submissions required for OMB review and approval prior to HRPO and IRB submissions. This was because we understood that OMB approval would be needed to obtain our initial sampling data from the Defense Manpower Data Center (DMDC), and because the OMB approval process typically takes longer than the IRB process. However, in a concurrent study, we were experiencing extended delays and considerable difficulties in connection with the DOD offices responsible for reviewing and forwarding PRA documentation to OMB. Ultimately, after multiple requests and discussions, the DOD Information Management Office determined that the study was *not* subject to the federal PRA and that no OMB approvals should be sought. However, since the present study includes a nationwide survey data collection, it was not clear whether it might fall under the PRA. We therefore petitioned DOD's Information Management Office to obtain a firm decision as to whether the project would be subject to OMB review and approval before undertaking the lengthy OMB review process. After multiple submissions and requests over many months, we obtained a ruling in June 2013 from officials at both the DOD Information Management Office and OMB indicating that the project did not fall under the PRA because the data collection had been grant-funded in response to a Baylor proposal, and was neither conducted by nor contracted out by the federal government. The project was therefore not subject to OMB review and approval.

The project encompasses two parallel data collections utilizing a multimodal survey effort that includes the national computer-assisted telephone interview (CATI) survey, as well as mail and online surveys. Data collection for the national CATI survey is to be conducted by our contractor, Westat. We initially understood that Westat would submit the telephone survey to its Institutional Review Board (IRB) for review and approval and therefore prepared human subjects' documentation for the telephone survey, as a separate project submission, to Baylor's IRB for approval. Baylor initial IRB approval for the telephone survey was obtained in September, 2013. After extended discussions and delays related to Westat's IRB process, we determined that Baylor IRB, as the lead institution, would provide all human subjects' oversight for the project. Baylor and Westat therefore worked out an IRB Authorization Agreement (IAA), under which Westat would defer IRB review for the project to Baylor IRB.

Because Baylor IRB would have sole oversight over the project, the Baylor Compliance Office asked that our submissions for all project data collections, including the mail and online surveys, be reviewed in conjunction with the CATI survey. Human subjects' documentation for the remaining portions of the project were submitted to Baylor IRB as an amendment and approved in May, 2014. Human subjects' documentation was initially submitted to the Army Office of Human Research Protections (HRPO) in June, 2014. Full human subjects approval for the project was provided by HRPO in August, 2014 (HRPO project # A-17630). All human subjects approvals continue to be current, with continuing review documents submitted to HRPO August 4, 2015.

Task 2. Obtain current data on the health status of 5,000 1991 Gulf War era veterans from a national, representative sample using a Computer Assisted Telephone Interview (CATI) Survey

Working with our contractors at Westat, all aspects of survey design and programming for the national CATI survey have been finalized. The contract services agreement with Westat was finalized in September, 2014, but remains on hold pending identification of a realistic start date for obtaining the required DOD data for the study, as described below, and initiating work on sampling and data collection.

We have not yet submitted the data request to DMDC to obtain information on 1990-1991 Gulf War era veterans for use in developing the national sample. This is due to a major setback encountered in two previous and separate studies that required us to obtain data from DMDC, including names and contact information for Gulf War era veterans in our target samples. These delays involve requirements raised by the DMDC Privacy Office in the Spring of 2014. In contrast to our prior experience and assurances involving DMDC data acquisition for use in federally-funded research studies, DMDC Privacy Office officials informed Baylor that DMDC data could only be approved for release to a federal entity and that the receiving IT system must be certified according to federal (e.g. FISMA, DIACAP) guidelines, or a corporate equivalent. Since that time, we have investigated multiple possible options for addressing these requirements, which had not been in place when we initially developed the project, nor after the project was funded by CDMRP. Possible solutions have included working with identified DOD collaborators and with partnering institutions or corporate entities to download and manage the DMDC data on a certified IT system. We are grateful for the input and extended efforts of our CDMRP Program Officer who worked with us to identify solutions. This included a potential partnership with the Army Analytics Group to facilitate access to the DMDC data needed for this project. However we learned in Spring 2015 that the Army Analytics Group was unable to work out a solution with DMDC and so could not assist us in accessing these data. We continue to work to develop a solution that will allow us to obtain the DMDC data for the project and to establish suitable IT security provisions that will support our use of these data in compliance with the new DMDC Privacy Office IT security requirements.

Study and instrument design for the CATI, mail, and online surveys have been finalized and we are ready to proceed with the CATI national survey. However, no activities have been

undertaken to initiate sampling and data collection, pending identification of suitable arrangements to allow our access to data providing location and contact information for 1991 Gulf War era veterans in order to establish our national sample.

The delays caused by our inability to obtain DMDC data have caused considerable uncertainty regarding the timeline for the project. The study was designed to allow our survey contractor, Westat, to receive the DMDC data since Westat routinely works with DMDC data utilizing its secure, DIACAP-certified data enclave. Even were that deemed acceptable, however, it is essential that we address DOD IT security requirements at our own institution in order to allow Westat to turn over DMDC information on veterans to Baylor so that we can develop the samples to be contacted for the mail and online surveys, and for data management and analyses.

Due to these and related challenges, we have worked to identify a new institutional affiliation that can provide a FISMA-certified IT system that supports the level of data security needed for housing DMDC data for this and other CDMRP-funded projects.

Note that no subject recruitment or data collection activities have been initiated and no research results are yet available.

Task 3. Obtain health data from a broad sample of at least 10,000 Gulf War era veterans via mail and web-based surveys and establish the 91 Veterans Research and Information Network (91VetNet)

In anticipation of receiving sampling information from DMDC, we previously finalized key aspects of study and instrument design for the mail and online surveys, which will be conducted in-house (that is, not through our contractor). This included work on practical aspects of implementation of the mail and online surveys, focusing on IT and execution details associated with launching the web survey and printing/mailing/scanning the mail survey

However, no subject recruitment or data collection activities have been initiated and no research results are yet available.

Tasks 4 – 5. Data Assembled and Analyzed; Preparation of Publications, Information Update, and Final Report

No activities completed or underway at this time. No data have been collected or analyzed, and no research results are yet available.

Key Research Accomplishments

Only regulatory submissions and work on finalizing study design and instruments have been accomplished to date. Data collection has not yet been initiated.

Reportable Outcomes

There are no manuscripts or other reportable outcomes at this time.

Conclusion

No research results are yet available; no conclusions can be drawn at this time.

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